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ON THE RED ALLY OF UROHÆMATOPORPHYRIN: A RETROSPECT OF TWELVE CASES.

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A case of disease is, from one point of view, a great physiological experiment performed by Nature, which often presents us with processes arrested and functions perverted at very instructive stages. The appearance in the urine of the pigment known as hæmatoporphyrin, or one of its allies, in place of the amber-coloured pigment normally there, is an example of an arrested process—that of katabolism of pigmentary matter derived from the blood, and taking place, on the largest scale, in the liver.

The term "urohæmatoporphyrin" dates from 1885, when MacMunn, in a paper[1] on the colouring matters of bile and urine, rechristened what he had five years earlier named "urohæmatin."[2] In 1880, in a case of rheumatic fever, he found "urohæmatin," and about the same date made it artificially by reduction of the pigment hæmatin. Urohæmatin was then found in a case of pericarditis, and on several occasions in the urine of Addison's disease. Since 1885 this pigment has always been known as urohæmatoporphyrin; it gives to urine an orange colour, and has been detected in a number of diseases, namely, in addition to the three given above—peritonitis, meningitis, cirrhosis of liver, peritoneal blood effusion, croupous pneumonia, typhoid fever, measles, and Hodgkin's disease.[3] [4]

In all these cases the colour of the urine, if not quite orange, is of a tint of amber deeper than the normal. Examined with the spectroscope, urohæmatoporphyrin shows a four-banded spectrum, the wave-lengths of whose bands are published in many of the above-mentioned monographs, but briefly put the bands are—one in the red to the left of D, two between D and E, and one near the F line. This spectrum closely resembles that of a laboratory pigment alkaline hæmatoporphyrin also four-banded, whose bands differ slightly from those of the urinary pigment in situation and intensity. Hæmatoporphyrin as a laboratory pigment has been long known both in acid and alkaline solutions. Thudichum in 1872 called it "cruentine."[5] The acid solution is two-banded and very characteristic, the pigment is iron-free. MacMunn found it in several of the lower animals, in the integument of certain slugs, star-fishes, the earth-worm, and in some birds' egg-shells.

Previously to 1890 this was all that could be said about hæmatoporphyrin and its urinary ally, but early in that year MacMunn saw for the first time two specimens (sent him by Dr. S. M. Copeman) of a "Burgundy-red urine" which contained no proteid, blood, or bile. Towards the close of the same year Mr. Cant of Lincoln, and Dr. Noël Paton of Edinburgh, each sent MacMunn a specimen of urine similarly pigmented.

Mr. Cant's case was that of a woman, aged 40, with exophthalmic goître, who had excreted red urine for three years (corpuscles 2,250,000 per c.mm. and HBO_2 40 per cent. of normal). She had taken a good deal of sulphonal. There was some patchy pigmentation of skin, and bullæ filled with a red alkaline fluid. To three of these urines Dr. Halliburton[7] alludes on p. 751 of his *Textbook* (1891), in a footnote, where he states that MacMunn regards this red pigment as "intermediate between urohæmatoporphyrin and hæmatoporphyrin." He refers the reader to two other similar cases (described by Drs. Ranking and Pardington[8]), which occurred

Fig. 1.—(1) Acid hæmatoporphyrin. (2) Alkaline hæmatoporphyrin. (3) Acid urohæmatoporphyrin. (4) Alkaline urohæmatoporphyrin. (5) Meio-de-oxyhæmatoporphyrin, or α-hæmatoporphyrin, the red ally of urohæmatoporphyrin. (Nos. 1 to 4 are from the charts accompanying MacMunn's paper *Journal of Physiology*, vol. x. No. 5 is from one of my own drawings)

in neurotic women and terminated fatally. The spectroscopic report on these two urines was made by Dr. MacMunn —the pigment was the same as in the first four cases, of deep garnet-red colour, yielding a four-banded spectrum resembling urohæmatoporphyrin, but differing, on careful comparison, in the position of the wave lengths of the absorption-bands: these were, however, not published, nor was the pigment named.

Two other cases of Burgundy-red urines were met with in 1890, both by Dr. Vaughan Harley[9]—one in Edinburgh (in the Royal Infirmary under Dr. John Wyllie), the other in Christiania. Both were of women who had been taking sulphonal, and who exhibited "nerve disturbances" and sleeplessness. The urine had no proteid, blood, or bile; in the foreign case the wave lengths of the centres of the absorption-bands were published: first band at λ562, second at

λ526, third at λ482, besides a feeble absorption in the violet.

On March 21st, 1891, Dr. Halliburton showed to the Physiological Society a specimen of red urine from a case of a lady, aged 30, who had excreted the pigment for seven weeks. She had been taking sulphonal since the previous November, and for more than a year had suffered from melancholic monomania. The urine was similar on examination to that of the former eight cases. The specimen was sent him by Drs. Blandford and Alliot, of Sevenoaks.

In 1894 Dr. Oswald,[10] then assistant-physician to the Glasgow Royal Asylum, watched a case of mania in a woman to whom large doses of sulphonal were given. Between April and August she took 2,200 grs. of sulphonal, and at intervals during that time excreted a "claret"-coloured urine, which had no bile and did not give the guiac test. Though the case was described as an example of hæmatoporphyrinuria, there is now no doubt that the pigment was not urohæmatoporphyrin, but the red ally of it.

In December, 1896, I saw for the first time a Burgundy-red urine, sent me from the wards in the Western Infirmary, Glasgow, from a patient under the care of Dr. McCall Anderson.[11]

The urine contained no proteid, sugar, blood, or bile, gave a four-banded spectrum convertible, after treatment with cold concentrated H_2SO_4, into the characteristic two-banded one of acid hæmatoporphyrin. This reaction the majority of the observers above alluded to had used with the same result. The case was that of a young fisherman, aged 25, from Stornoway, who had suffered annually from April to October from an eruption of a vesicular kind to which at first the name dermatitis herpetiformis bullosa was given, but which was subsequently named hydroa æstivale. His corpuscles were normal in number, but his HbO_2 only 60 per cent. of normal.

In August, 1897, I was sent from the same wards a second specimen of dark red urine with a note saying it was being passed by the brother of the man who had been a patient in December, 1896.[12] His urine was precisely similar to that of his brother, and in it, without any dilution, I measured the wave lengths of the four bands of absorption which are in millionths of a millimetre.

First band (in red) from λ638 to λ620, centre at λ630.
Second band (orange region) from λ586 to λ551, centre at λ563.
Third band (green region) from λ538 to λ522, centre at λ530
Fourth band (near green-blue junction) from λ517 to λ490 or λ488, the righthand edge is hazy, and varies with the dilution, centre about λ498, besides considerable absorption in the violet.

Comparing these bands with those above detailed as published by Harley, we find that in the pigment he described no band to the left of D, that is in the red, was found. I regard this as very peculiar, since every kind of hæmatoporphyrin has a band in the red region, its exact position varying with the different pigments. In acid hæmatoporphyrin and acid urohæmatoporphyrin it is very close to D; in the two alkaline solutions of these, respectively, it is farther from D, while in the case of the red ally it is most distant of all from D. On diluting the solution it quickly disappears. All that I can suggest is, either that there was less pigment per cent. present in the foreign case or that it was diluted for the examination. There can be no doubt that it was this red α-hæmatoporphyrin. I would say a band in the red was one

of the characteristic features of the absorption-spectra of all the hæmatoporphyrins.

Being led to reflect upon the genetic relationship of these pigments to those of bile and urine,[13] I found it awkward not to have a name for the red ally of urohæmatoporphyrin, and so devised one which endeavoured to express what MacMunn believed to be its position relative to hæmatoporphyrin and urohæmatoporphyrin, namely, its being intermediate as a reduction product, between the two. I therefore named it meio-de-oxyhæmatoporphyrin. It might, however, be well to call it by a term that connoted no particular view as to its origin, so that the red pigment might be merely known as α-hæmatoporphyrin and the orange one as β-hæmatoporphyrin. In a sense they are *both uro*hæmatoporphyrins probably in different stages of reduction.

Of the twelve cases mentioned, seven have been in women, and in four of these, sulphonal had been administered. In all there was grave nervous disturbance. Of these seven cases, five were fatal. Having already discussed, to some extent, elsewhere, the seat of origin of these pigments, I refrain from again entering upon that topic, but would only say that the liver is probably the chief seat of the abnormal katabolism of blood pigment through hæmataporphyrin (iron-free) to the iron-free pigments of bile and urine. Had I not seen Professor McCall Anderson's first case, in which the excretion of red pigment has recurred for years and the man is still living, I should say this red urohæmatoporphyrinuria was a most grave symptom, a precursor of a fatal issue—such at any rate it seems to be in the case of women.

I ought to add that α-hæmatoporphyrin is very stable. In the first specimen of it, which I received a year ago, the pigment has preserved its chemical and spectroscopic integrity. In this respect it is exactly like laboratory acid hæmatoporphyrin which never seems to decompose. Its presence has also some power in greatly retarding the putrefaction of the urine itself.

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